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(57) Abstract

The invention relates to a process for synthesizing piperazic acid and similar, ring–containing acids. The invention also relates to a process for simultaneously N(2)–acylating piperazic acid or an ester thereof and forming a bicyclic ring structure. The invention also relates to the use of either or both processes in a method of synthesizing a bicyclic compound useful as an intermediate for the production of an inhibitor of a caspase, particularly an inhibitor of interleukin– β converting enzyme ("ICE").

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PROCESS FOR PREPARING PIPERAZIC ACID AND ITS CONVERSION TO N-ACYLATED BICYCLIC RINGS CONTAINING N,N-LINKAGES USEFUL AS INTERMEDIATES FOR CASPASE INHIBITORS

AN INTERMEDIATE IN THE MANUFACTURE OF A CASPASE INHIBITOR

TECHNICAL FIELD OF THE INVENTION

The invention relates to a process for synthesizing piperazic acid and similar, ring-containing acids. The invention also relates to a process for simultaneously N(2)-acylating piperazic acid or an ester thereof and forming a bicyclic ring structure. The invention also relates to the use of either or both processes in a method of synthesizing a bicyclic compound useful as an intermediate for the production of an inhibitor of a caspase, particularly an inhibitor of interleukin-1ß converting enzyme ("ICE").

BACKGOUND OF THE INVENTION

Piperazic acid derivatives are important intermediates in natural product synthesis and in the synthesis of biologically useful non-natural amino acids and peptidomimetics (e.g., inhibitors described in PCT publications WO 97/22619 and WO 95/35308). Several syntheses of piperazic acid and derivatives thereof have been described [Decicco et al., Syn. Lett., p. 615 (1995); Schmidt et al., Synthesis, p. 223 (1996); Rutjes et al., Tetrahedron, p. 8605 (1993); PCT publications WO 97/22619 and WO 95/35308). In each case however, the synthesis requires multiple steps, utilizes expensive reagents and produces less than desirable yields.

Compounds containing a bicyclic, aza-containing ring systems have been prepared as conformationally restricted dipeptide surrogates for a variety of medically important compounds. In particular, such ring systems are present in angiotensin converting enzyme (ACE) inhibitors, such as Cilazapril®, and in caspase inhibitors, such as inhibitors of interleukin-1 converting enzyme (ICE).

Current methods for synthesizing compounds containing these byciclic aza-containing ring systems have many disadvantages. The typical methods of forming this ring system have been described [EP 94,095, WO 95/35308, WO 97/22619, United States patents 5,656,627, 5,716,929 and 5,756,486 and J. P. Kim, et al., Tetrahedron Letters, 38, pp. 4935-4938 (1997)].

These methods involve coupling an appropriately protected amino acid with the appropriately N(1)-protected piperazic acid or ester. After deprotection, the bicyclic system is then formed via an acid chloride coupling at the N(1) position.

The main disadvantages to such methods are the use of expensive reagents and the number of steps required for protection and deprotection making the overall process extremely time consuming. Moreover, these methods are often useful for research purposes but are not amenable to large scale production.

In order to be more commercially feasible, it would be desirable to produce compounds containing a byciclic aza-containing ring system in an easier, less expensive manner than has been previously described.

SUMMARY OF THE INVENTION

Applicant has solved the problems indicated above by providing: 1) a new method for synthesizing piperazic acid; and 2) a new method of simultaneously N(2)-acylating an N(1)-protected piperazic acid or an ester thereof and creating a bicyclic ring structure comprising that acylated piperazic acid or ester.

The first method involves treating a 1,4-dihaloalkyl ester with an N,N'-bis-protected hydrazine dissolved in DMF in the presence of a water scavenger, a metal hydroxide and a phase transfer catalyst. This method produces surprisingly increased yield of the desired protected piperazic acid.

The second method involves the formation of the desired bicyclic system in two, simple steps. This method also utilizes inexpensive reagents, does not require selective protection/deprotection, and is quite amenable to large scale production. Moreover, this method produces very little contaminating by-products. This method also preserves chirality between the N(1)-protected piperazic or similar acid or an ester thereof and the resulting byciclic aza-containing ring system.

This method is particularly useful for producing an intermediate that may be subsequently converted into a caspase inhibitor, particularly an inhibitor of ICE, through additional steps known in the art.

DETAILED DESCRIPTION OF THE INVENTION

Some of the abbreviations used throughout the specifications (including in chemical formulae) are:

Bu = butyl

Et = ethyl

Cbz = carboxybenzyl

DMF = N,N-dimethylformamide

THF = tetrahydrofuran

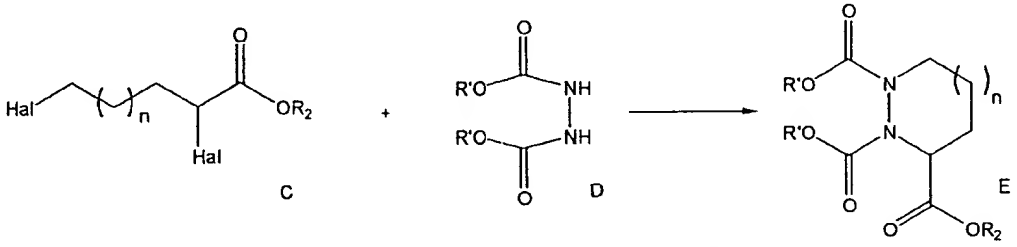
MTBE = methyl tert-butyl ether

DCC = dicyclohexyl carbodiimide

EDC = 1-(3-Dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride

Ac = acetyl.

According to one embodiment, the invention provides a process for producing compound E by reacting compounds C and D:



comprising the steps of:

a) dissolving compounds C and D together in DMF;

b) adding to said solution of C and D:

i) a water scavenger;

ii) a metal hydroxide selected from LiOH, NaOH or KOH; and

iii) a phase transfer catalyst

c) allowing the mixture produced in step b) to react at room temperature for 2 to 48 hours;

d) adding an organic solvent and water to said mixture to create an aqueous phase and an organic phase; and

e) purifying compound E from said organic phase;

wherein:

R_2 is selected from hydrogen, C1-C6 straight or branched alkyl; C2-C6 straight or branched alkenyl or alkynyl C1-C6 alkyl or Ar, wherein said alkyl, alkenyl or alkynyl is optionally substituted with Ar;

n is 0 or 1;

"Hal" is any halogen; and

each R' is an independently selected carboxyl protecting group

The water scavenger referred to above may be selected from any water scavengers known in the art. These include, but are not limited to, Na_2SO_4, $MgSO_4$, and molecular sieves. Preferably, the water scavenger is sodium sulfate.

According to another preferred embodiment, the metal hydroxide used in the above method is LiOH.

The phase transfer catalyst referred to in the above method may also be selected from any such catalysts known in the art. These include, but are not limited to, Bu_4NI, Aliquat 336 (Aldrich Chemicals) and other quartenary ammonium salts. Preferably, the catalyst is Bu_4NI.

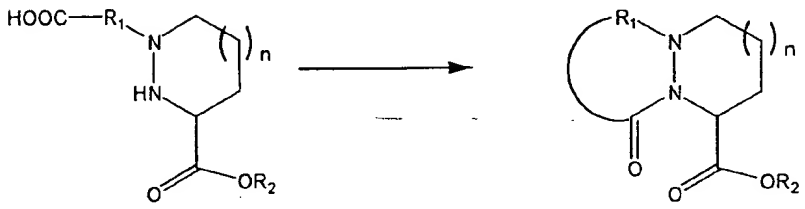
According to another preferred embodiment, n is 1.

According to yet another preferred embodiment, each Hal is Br.

In yet another preferred embodiment of the method set forth above, R_2 is t-butyl.

In another preferred embodiment, R' is benzyl.

According to another embodiment, the invention provides a process for converting compound G to compound H:



G H

wherein:

R_1 is a C2-C4 straight chain alkyl optionally substituted at any carbon with one or more substituents selected from C1-C6 straight or branched alkyl, C2-C6 straight or branched alkenyl or alkynyl, O-C1-C6 straight or branched alkyl, O-C2-C6 straight or branched alkenyl or alkynyl, oxo, halo, NO_2, $N(R_4)(R_4)$, CN, Ar or O-Ar;

R_2 is selected from hydrogen, C1-C6 straight or branched alkyl, C2-C6 straight or branched alkenyl or alkynyl C1-C6 alkyl or Ar, wherein said alkyl, alkenyl or alkynyl is optionally substituted with Ar;

n is 0 or 1;

Ar is a saturated, partially saturated or unsaturated monocyclic or bicyclic ring structure, wherein each ring contains 5 to 7 ring atoms and each ring optionally contains from 1 to 3 heteroatoms selected from O, N and S;

wherein Ar is optionally substituted at one or more ring atoms with one or more substituents independently selected from C1-C6 straight or branched alkyl, C2-C6 straight or branched alkenyl or alkynyl, O-C1-C6 straight or branched alkyl, O-C2-C6 straight or branched alkenyl

or alkynyl, oxo, halo, NO_2, $N(R_4)(R_4)$, CN, Ar_1, O-Ar_1; wherein

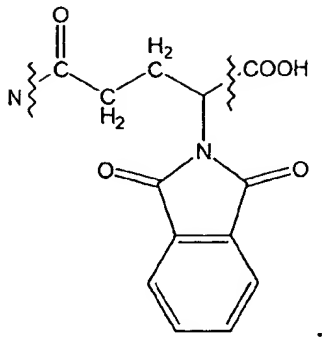
Ar_1 is a saturated, partially saturated or unsaturated monocyclic or bicyclic ring structure, wherein each ring contains 5 to 7 ring atoms and each ring optionally contains from 1 to 3 heteroatoms selected from O, N and S; and

each R_4 is independently selected from H or an amino protecting group, with the proviso that both R_4 are not simultaneously hydrogen.

The term "amino protecting group", as used herein, means a moiety that prevents chemical reactions from occurring on the nitrogen atom to which that protecting group is attached. An amino protecting group must also be removable by a chemical reaction.

In one preferred embodiment, R_1 is substituted at the terminal carbon bound to the -COOH moiety with a protected amine. The term "protected amine" as used herein, means a nitrogen-containing moiety which can be chemically modified to an amine.

In another preferred embodiment, R_1 is substituted at the other terminal carbon (i.e., the one bound to the ring nitrogen) with oxo, making R_1 an acyl-containing moiety. More preferred is when R_1 contains both the protected amine substituent and the oxo substituent. One of the most preferred R_1 groups is:



In another preferred embodiment, n is 1.

In yet another preferred embodiment, R_2 is t-butyl.

The method of this invention comprises the steps of:

(a) suspending compound G in an organic solvent selected from dichloroethane, dichloromethane, toluene, chlorobenzene, chloroform, monoglyme, diglyme or CCl_4;

(b) adjusting the temperature of the resulting solution to between 20°C and 100°C;

(c) adding base and more than about 1 equivalent of RSO_pCl_p to said solution, wherein R is absent or is selected from C1-C6 straight or branched alkyl or Ar, and each p is independently 1 or 2; and

(d) allowing the reaction to proceed over a period of between 2 and 24 hours.

Not all organic solvents may be used to dissolve compound G in step (a). The list of solvents set forth above are known to work. Other similar organic solvents may also work in the reaction and are to be considered part of the present invention. Preferably, the organic solvent is toluene or dichloroethane.

Step (b) is preferably carried out at about 70°C.

According to a alternate embodiment, in step (c), less than about 0.2 equivalents of N,N-dimethylformamide may also added.

In another preferred embodiment of step (c), RSO_pCl_p is selected from methanesulfonyl chloride or $SOCl_2$. Preferably, in step (c), about 1 to 3 equivalents of RSO_pCl_p are added.

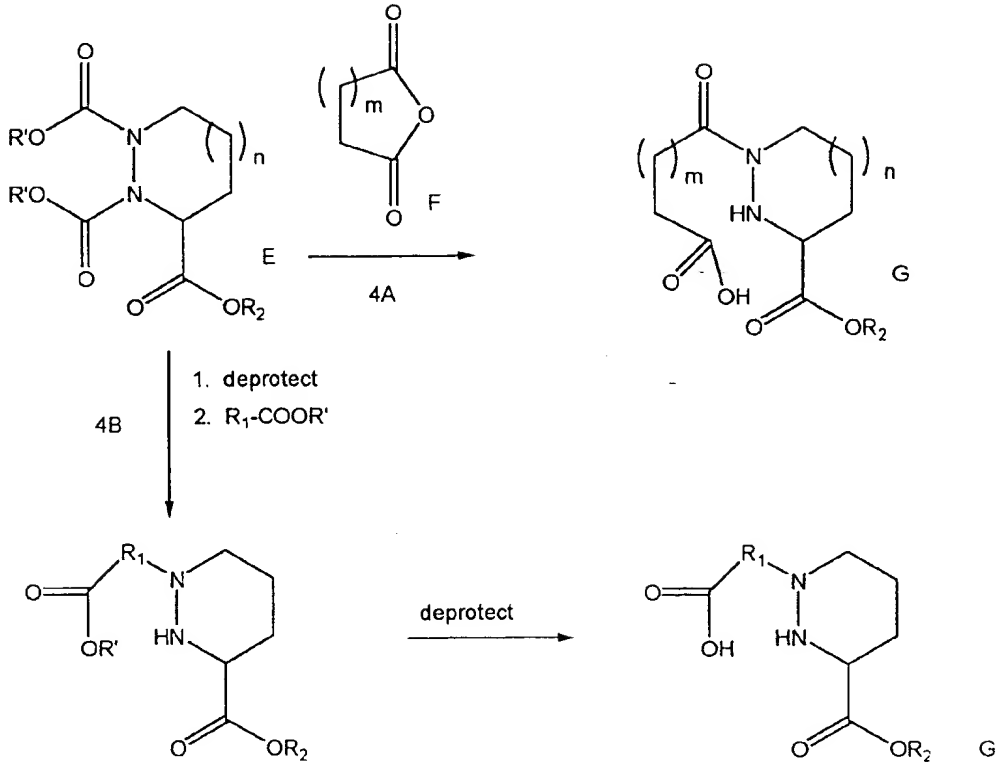
According to yet another preferred embodiment of step (c), about 2 to 4 equivalents of base are added to the reaction. Preferably, the base is selected from pyridine, collidine, lutidine, $NaHCO_3$, imidazole, triethylamine, N-methylmorpholine, diisopropylethylamine or K_2CO_3. Most preferably, the base is 2,6-lutidine.

In step (c), the base and the RSO_pCl_p are added simultaneously and may be added all at once to the reaction or gradually over period of time up to 3 hours.

Once the reaction is complete, we prefer to purify compound H by diluting the reaction with an organic solvent and then washing the solution first with $NaHCO_3$ and then with brine. The solution is then dried over Na_2SO_4 and concentrated.

Compound G may be obtained from compound E. That conversion may be achieved in one of two ways depicted below in Scheme 2, depending upon the nature of R_1.

Scheme 1

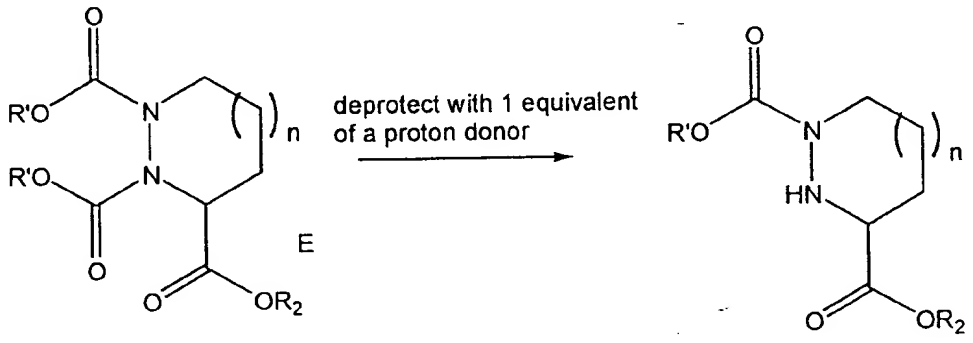


In Scheme 1, m is 0, 1 or 2; and n, R', R_1 and R_2 are as defined above. Also, in compound F any of the unsubstituted ring carbon atoms may be optionally substituted by one or more substituents independently selected from C1-C6 straight or branched alkyl, C2-C6 straight or branched alkenyl or alkynyl, O-C1-C6 straight or branched alkyl, O-C2-C6 straight or branched alkenyl or alkynyl, oxo, NO_2, $N(R_4)(R_4)$, CN, Ar, or O-Ar, wherein said alkyl, alkenyl or alkynyl is optionally substituted with Ar, and wherein R_4 and Ar are as defined above.

Reaction 4A comprises stepwise deprotection and acylation (which can be performed in the same reaction vessel) if the carboxyl protecting groups can be removed by hydrogenolysis, (e.g., if the protecting group is benzyl) or utilizing transfer hydrogenation conditions.

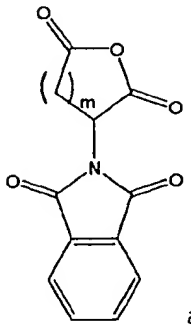
If not, a deprotection step must precede the addition of the anhydride for the acylation reaction.

In order to completely deprotect at both nitrogens under transfer hydrogenation conditions, at least 2 equivalents of the proton donor (e.g., Et_3SiH) must be added. If only one equivalent of the proton donor is added, deprotection occurs selectively at the N(2) nitrogen:



The resulting N(1) protected compound is also useful as an intermediate in producing medically important compounds, such as the ICE inhibitors described herein and in PCT publications WO 97/22619 and WO 95/35308. Thus, this reaction to produce an N(1) protected compound is also an embodiment of the present invention.

When compound F contains substituents and is not symmetrical, reaction 4A produces mixtures of compounds, wherein acylation of the N(1) nitrogen may occur at either C(O) functionality. This may be avoided by using substituents that favor the formation of the desired product. For example, in reaction 4A, the use of:



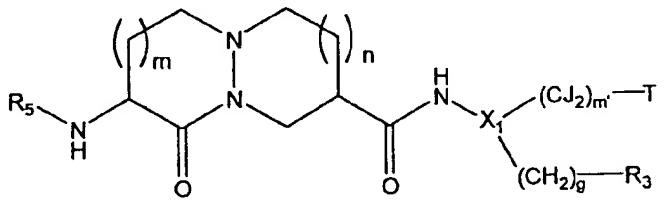
as compound F forces the formation of a compound wherein acylation of the N(1) nitrogen occurs at the C(O) functionality furthest away from the pthalimide substituent.

In order to avoid an unwanted reaction at the N(2) nitrogen in step 4B, the two carboxy protecting groups (R') on compound E should be different, such that the N(1) protecting group (-COOR') can be selectively removed without removing the N(2) protecting group.

The creation of intermediate E can be achieved by standard syntheses known in the art. More preferably, intermediate E is synthesized by reacting compounds C and D according to the method of this invention as set forth above.

Intermediate compound G containing the protected amine on R_1, and its subsequent conversion to compound H, may serve as the key intermediate and synthesis step, respectively, in an improvement in the synthesis of known caspase inhibitors, particularly inhibitors of interleukin-1 converting enzyme ("ICE"), such as those described in United States patents 5,716,929, 5,656,627, and 5,756,466 and in PCT publications WO 95/35308 and WO 97/22619.

Those inhibitors have the general formula (I):



(I)

wherein:

any ring is optionally substituted at any carbon by Q_1, at any nitrogen by R_5, and at any atom by =O, -OH, -COOH, or halogen;

X_1 is CH or N;

g is 0 or 1;

m and m' are independently 0, 1 or 2;

n is 0 or 1;

each J is independently selected from -H, -OH, or -F, provided that when a first and a second J are bound to a C, and said first J is -OH, then said second J is -H;

T is $-Ar_3$, -OH, $-CF_3$, -C(O)-C(O)-OH, -C(O)-OH or any biosteric replacement for -C(O)-OH;

R_3 is -CN, $-CH=CH-R_9$, $CH=N-O-R_9$, $-(CH_2)_{1-3}-T_1-R_9$, $-CJ_2-R_9$, $-C(O)-R_{13}$, or $-C(O)-C(O)-N(R_5)(R_{10})$;

T_1 is -CH=CH-, -O-, -S-, -SO-, $-SO_2-$, $-NR_{10}-$, $-NR_{10}-C(O)-$, -C(O)-, -O-C(O)-, -C(O)-O-, $-C(O)-NR_{10}-$, $O-C(O)-NR_{10}-$, $-NR_{10}-C(O)-O-$, $-NR_{10}-C(O)-NR_{10}-$, $-S(O)_2-NR_{10}-$, $-NR_{10}-S(O)_2-$ or $-NR_{10}-S(O)_2-NR_{10}-$;

each R_5 is independently selected from -H, $-Ar_1$, $-C(O)-Ar_1$, $-S(O)_2-Ar_1$, $-R_9$, $-C(O)-NH_2$, $-S(O)_2-NH_2$, $-C(O)-R_9$, $-C(O)-O-R_9$, $-S(O)_2-R_9$, $-C(O)-N(R_{10})(Ar_1)$, $-S(O)_2-N(R_{10})(Ar_1)$, $-C(O)-N(R_{10})(R_9)$, or $-S(O)_2-N(R_{10})(R_9)$;

each R_9 is a C_{1-6} straight or branched alkyl group optionally singly or multiply substituted with -OH, -F,

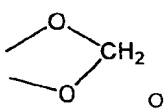
=O or Ar_1, wherein any R_9 may be substituted with a maximum of two Ar_1;

each R_{10} is independently selected from -H or C_{1-6} straight or branched alkyl;

R_{13} is -H, $-Ar_1$, $-R_9$, $-T_1-R_9$ or $-(CH_2)_{1-3}-T_1-R_9$;

each Ar_2 is a cyclic group independently selected from a monocyclic, bicyclic or tricyclic aryl group containing 6, 10, 12 or 14 carbon atoms; a monocyclic, bicyclic or tricyclic cycloalkyl group containing between 3 and 15 carbon atoms, said cycloalkyl group being optionally benzofused; or a monocyclic, bicyclic or tricyclic heterocycle group containing between 5 and 15 ring atoms and at least one heteroatom group selected from -O-, -S-, -SO-, $-SO_2-$, =N-, or -NH-, wherein said heterocycle group optionally contains one or more double bonds and optionally comprises one or more aromatic rings;

Ar_3 is a cyclic group selected from phenyl, a 5-membered heteroaromatic ring or a 6-membered heteroaromatic ring, wherein said heteroaromatic rings comprise from 1-3 heteroatom groups selected from -O-, -S-, -SO-, $-SO_2-$, =N-, or -NH-;

wherein each Ar_1 or Ar_3 is optionally singly or multiply substituted at any ring atom by $-NH_2$, -C(O)-OH, -Cl, -F, -Br, -I, $-NO_2$, -CN, =O, -OH, -perfluoro C_{1-3} alkyl,  or $-Q_1$; and

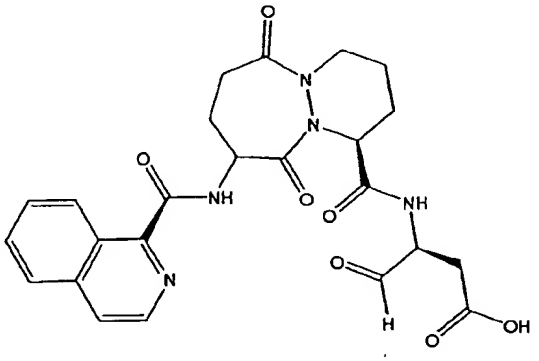
each Q_1 is independently selected from $-Ar_1$, $-R_9$, $-T_1-R_9$, or $(CH_2)_{1-3}-T_1-R_9$; provided that when $-Ar_1$ is substituted with a Q_1 which comprises one or more additional $-Ar_1$ groups, said additional $-Ar_1$ groups are not substituted with Q_1.

Preferably, the process of this invention is used as a step in the synthesis of a compound of formula I, wherein n is 1 and m is 2.

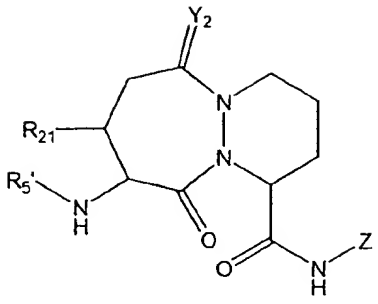
In another preferred embodiment, the process of this invention is used as a step in the synthesis of a compound of formula I, wherein R_5 is an acyl moiety selected from $-C(O)-Ar_1$, $-C(O)-NH_2$, $-C(O)-R_9$, $-C(O)-O-R_9$, $-C(O)-N(R_{10})(Ar_1)$, or $-C(O)-N(R_{10})(R_9)$.

In yet another preferred embodiment, the process of this invention is used as a step in the synthesis of a compound of formula I, wherein X_1 is CH; each J is H; m' is 1; T is -COOH or a biosteric replacement for -COOH; g is 0; and R_3 is $-C(O)-R_{13}$.

In the most preferred embodiment of using the process of this invention as a step in the synthesis of a compound of formula I, said compound has the structure:

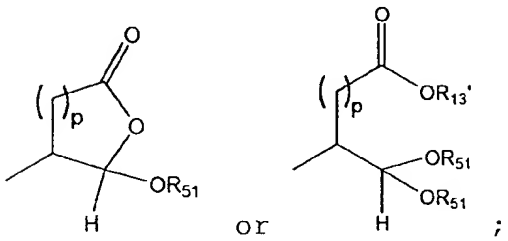


Alternatively, the process of this invention may be used as a step in the synthesis of a compound of the formula (II):



II; wherein:

Z is selected from



;

p is 1 or 2;

each $R_{5'}$ is independently selected from $-C(O)-R_{13'}$, $-C(O)O-R_{9'}$, $-C(O)-N(R_{10'})(R_{10'})$, $-S(O)_2-R_{9'}$, $-S(O)_2-NH-R_{10'}$, $-C(O)-CH_2-O-R_{9'}$, $-C(O)C(O)-R_{10'}$, $-R_{9'}$, $-H$, $-C(O)C(O)-OR_{10'}$, or $-C(O)C(O)-N(R_{9'})(R_{10'})$;

each $R_{9'}$ is independently selected from $-Ar_1$ or a $-C_{1-6}$ straight or branched alkyl group optionally substituted with Ar_1, wherein the $-C_{1-6}$ alkyl group is optionally unsaturated;

each $R_{10'}$ is independently selected from $-H$, $-Ar_1$, a $-C_{3-6}$ cycloalkyl group, or a $-C_{1-6}$ straight or branched alkyl group optionally substituted with $Ar_{3'}$, wherein the $-C_{1-6}$ alkyl group is optionally unsaturated;

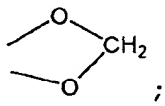
$R_{13'}$ is selected from H, Ar_1, or a C_{1-6} straight or branched alkyl group optionally substituted with Ar_1, $-CONH_2$, $-OR_{5'}$, $-OH$, $-OR_{9'}$, or $-CO_2H$;

each R_{51} is independently selected from $R_{9'}$, $-C(O)-R_{9'}$, $-C(O)-N(H)-R_{9'}$, or two R_{51} taken together form a saturated 4-8 member carbocyclic ring or heterocyclic ring containing -O-, -S-, or -NH-;

each R_{21} is independently selected from -H or a $-C_{1-6}$ straight or branched alkyl group;

Y_2 is $-H_2$ or =O

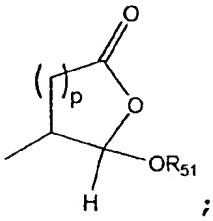
each Ar_1 is a cyclic group independently selected from the set consisting of an aryl group which contains 6, 10, 12, or 14 carbon atoms and between 1 and 3 rings and an aromatic heterocycle group containing between 5 and 15 ring atoms and between 1 and 3 rings, said heterocyclic group containing at least one heteroatom group selected from -O-, -S-, -SO-, SO_2, =N-, and -NH-, said heterocycle group optionally containing one or more double bonds, said heterocycle group optionally comprising one or more aromatic rings, and said cyclic group optionally being singly or multiply substituted by $-Q_1$;

each Q_1 is independently selected from the group consisting of $-NH_2$, $-CO_2H$, -Cl, -F, -Br, -I, $-NO_2$, -CN, =O, -OH, -perfluoro C_{1-3} alkyl, $R_{5'}$, $-OR_{5'}$, $-NHR_{5'}$, $OR_{9'}$, $-N(R_{9'})(R_{10'})$, $R_{9'}$, $-C(O)-R_{10'}$, and  ; provided that when $-Ar_1$ is substituted with a Q_1 group which comprises one or more additional $-Ar_1$ groups, said additional $-Ar_1$ groups are not substituted with another $-Ar_1$.

Preferably, the process of this invention is used as a step in the synthesis of a compound of formula II, wherein Y_2 is O and R_{21} is H.

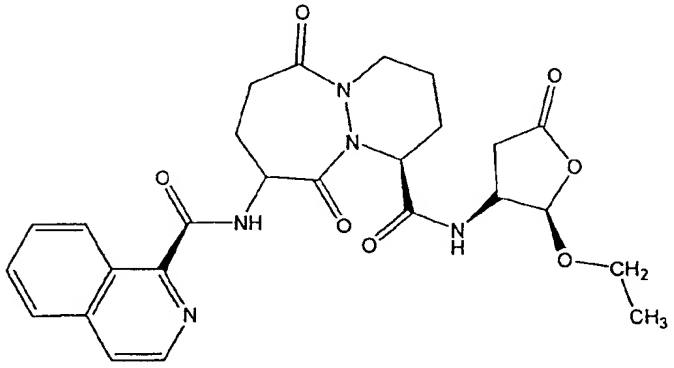
In another preferred embodiment, the process of this invention is used as a step in the synthesis of a compound of formula II, wherein $R_{5'}$ is selected from $-C(O)-R_{10'}$, $-C(O)O-R_{9'}$, $-C(O)-N(R_{10'})(R_{10'})$, $-C(O)-CH_2-O-R_{9'}$, $-C(O)C(O)-R_{10'}$, $-C(O)C(O)-OR_{10'}$, or $-C(O)C(O)-N(R_{9'})(R_{10'})$.

In yet another preferred embodiment, the process of this invention is used as a step in the synthesis of a compound of formula II, wherein Z is

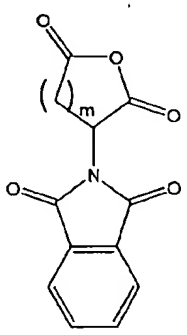


; p is 1 and R_{51} is selected from $-Ar_1$, $-C_{1-6}$ straight or branched alkyl or $-C_{1-6}$ straight or branched alkyl substituted with Ar_1.

In the most preferred embodiment of using the process of this invention as a step in the synthesis of a compound of formula II, said compound has the structure:



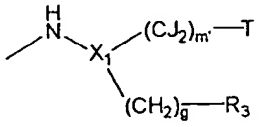
In the synthesis of these inhibitors, the terminal carbon of R_1 adjacent the -COOH moiety contains a protecting substituent. Preferably that protecting substituent is



.

The synthesis steps from compound H to the inhibitors set forth above involve removal of the

protecting substituent on R_1; coupling of the R_5-NH- or $R_{5'}$-NH- moiety in its place; hydrolysis of the R_2 group;

and coupling of the amine ( or -NH-Z)

in its place.

The removal of the protecting substituent on R_1 is typically carried out with hydrazine. The subsequent coupling of the R_5-NH- or $R_{5'}$-NH- moiety is achieved with standard coupling reagents, such as EDC, DCC or acid chloride.

Depending upon the nature of R_2, its hydrolysis may be achieved with an acid (when R_2 is t-butyl), a hydroxide (when R_2 is any other alkyl, alkenyl or alkynyl or Ar) or hydrogenolysis (when R_2 is an Ar-substituted alkyl, alkenyl or alkynyl). This produces the corresponding acid from the ester.

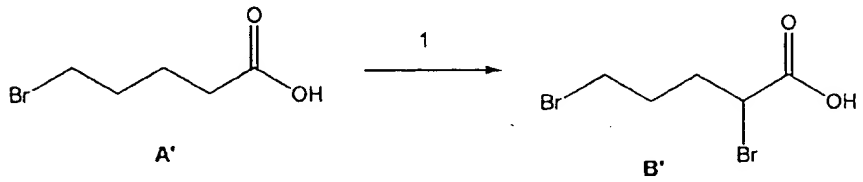
The acid is then coupled to the amine with standard coupling reagents, such as EDC, DCC or acid chloride.

In order that this invention be more fully understood, the following examples are set forth. These examples are for the purpose of illustration only and are not to be construed as limiting the scope of the invention in any way.

EXAMPLE 1

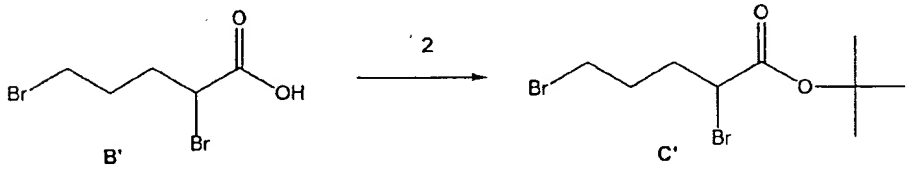
Synthesis of a 7,6 Scaffold for a Caspase Inhibitor

A.



Compound A' was dissolved in 5 equivalents of $SOCl_2$ and then heated to 80°C for 1 hour. The solution was then cooled to 50°C and 2 equivalents of bromine were added. The solution was incubated at 50°C for an additional 12 hours until the red color disappeared. We then cooled the solution to 10°C and added 4 volumes of water. The solution was then re-heated to 50°C for another hour. We then separated the organic and aqueous layer, washed the organic layer consecutively with water, Na_2SO_3 and then brine, removing the aqueous layer after each washing. The final organic layer was then isolated, dried over Na_2SO_4 and concentrated to produce compound B' as an amber oil.

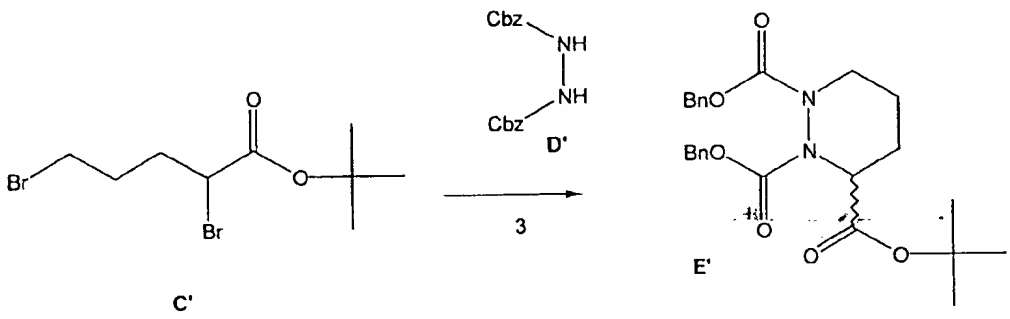
B.



Compound B' was treated with 1 equivalent of *tert*-butanol and 0.1 equivalents of 4-(dimethylamino)-pyridine in a solution of and the resulting solution cooled to 7°C. We then added a solution of 1 equivalent of DCC in toluene while maintaining reaction temperature at less than 22°C. The cooling bath was removed and the

reaction was stirred at ambient temperature under a nitrogen atmosphere for 16 hours. The reaction mixture was then diluted with hexane and cooled to 9°C. The resulting solids were removed by filtration. The filtrate was washed consecutively with 0.1N HCl, water, and then sodium bicarbonate. The filtrate was then dried over sodium sulfate and concentrated *in vacuo* to afford compound C' as a yellow oil.

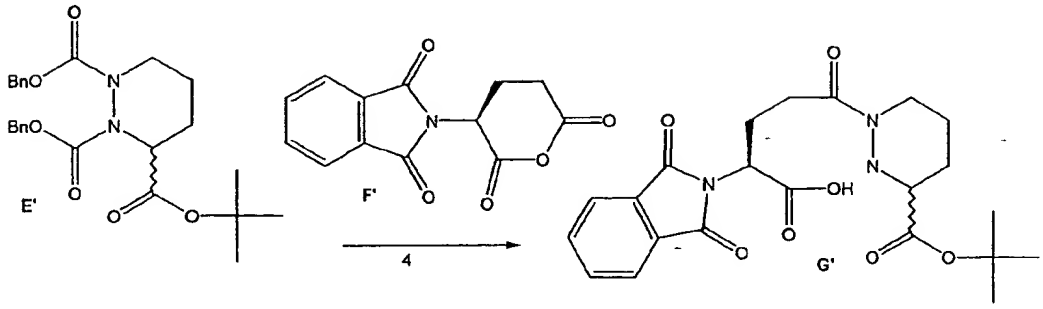
C.



Compound D' was combined with 1.2 equivalents of compound C' and dissolved in DMF at ambient temperature under nitrogen atmosphere. We then added granular sodium sulfate, 2.5 equivalents of LiOH monohydrate, and then 0.1 equivalents Bu_4NI to the resulting solution. The reaction temperature was maintained at between 20°C and 30°C and allowed to stir for 16 hours. The reaction mixture was then diluted with ethyl acetate and water and the layers separated. The organic layer was washed with water and then brine, dried over sodium sulfate and concentrated *in vacuo* to produce an amber oil. This oil was then dissolved in 5 volumes of ethanol at ambient temperature. We then added 2.5 volumes of water. The resulting mixture was allowed to stir until a white solid formed (approximately 5 hours).

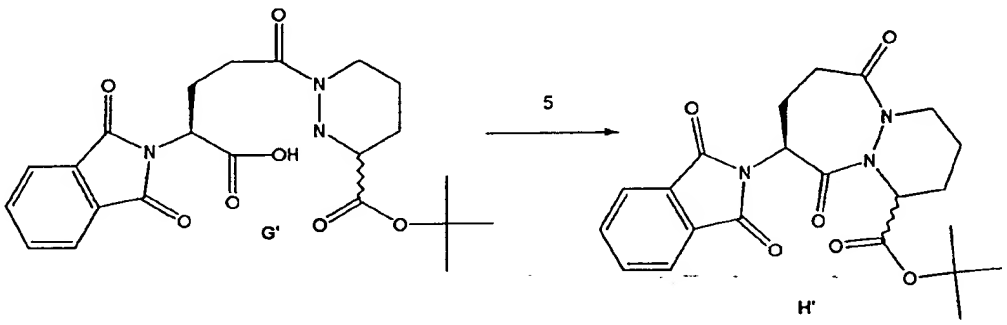
The crystallized product was isolated via filtration then dried *in vacuo* to afford compound E′ as a white solid.

D.



We dissolved compound E′ in THF. We then added, at ambient temperature under a nitrogen atmosphere, 0.02 equivalents of triethylamine and 0.01 equivalents of $Pd(OAc)_2$. A solution of 2.5 equivalents of triethylsilane (Et_3SiH) in THF was then added and the resulting black solution was allowed to stir for 16 hours to complete the reaction. We then added a saturated, aqueous solution of sodium bicarbonate followed by a solution of compound F′ in THF. After 30 minutes, the layers were separated and the aqueous layer acidified to pH 4.5 with aqueous citric acid. The product in the aqueous layer was then extracted into ethyl acetate. The organic layer was isolated, washed with brine, dried over sodium sulfate and concentrated *in vacuo* to produce a white foam. This crude product was then recrystallized from MTBE to afford compound G′ as a white powder.

E.



Method #1:

To a suspension of compound G' and 0.1 equivalents of DMF in dichloroethane, at 70°C we added 5 equivalents of 2,6-lutidine simultaneously with 2.5 equivalents of $SOCl_2$ over a period of 3 hours. The reaction was then diluted with toluene and washed consecutively with $NaHCO_3$ and brine. The solution was then dried over Na_2SO_4 and concentrated *in vacuo* to afford compound H' as a yellow solid.

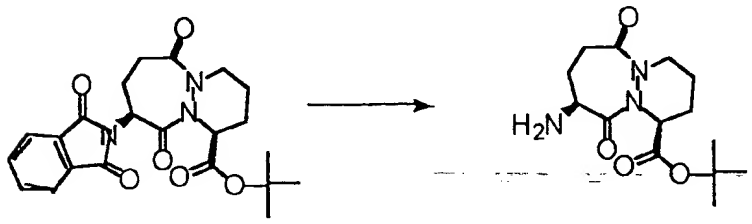
Method #2:

To a suspension of compound G' in dichloroethane, at 70°C, we added 4 equivalents of 2,6-lutidine followed by 2 equivalents of methanesulfonyl chloride. The resulting solution was stirred at 70°C for 12 hours. The reaction was then diluted with toluene and washed consecutively with $NaHCO_3$ and brine. The solution was then dried over Na_2SO_4 and concentrated *in vacuo* to afford compound H' as a white solid. Method #2 produced a significantly higher yield of H' as compared to Method #1.

EXAMPLE 2

Use of Intermediate H' to Produce an Inhibitor of ICE

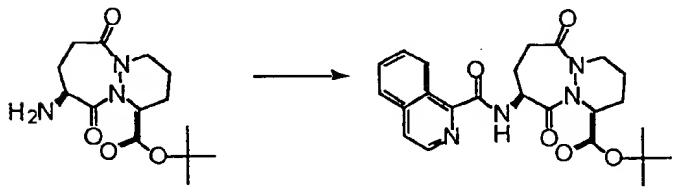
A.



H' I'

t-Butyl-9-amino-6, 10-dioxo-1,2,3,4,7,8,9,10-octahydro-6-H-pyridazino[1,2-a][1,2] diazepine-1-carboxylate (GB 2,128,984) To a suspension of H' (107 g, 0.25 mol) in ethanol (900 mL) was added hydrazine (27 mL, 0.55 mol) and the resulting mixture was allowed to stir at ambient temperature. After 4 hours, the reaction was concentrated *in vacuo* and the resulting white solid was suspended in acetic acid (1L of 2N) and allowed to stir at ambient temperature for 16 hours. The resulting white solid was filtered off and washed with water. The filtrate was made basic by the addition of solid sodium carbonate and the product extracted with dichloromethane. The organic layer was washed with brine, dried over magnesium sulfate and concentrated *in vacuo* to afford 79 mg of compound I' as a yellow viscous oil.

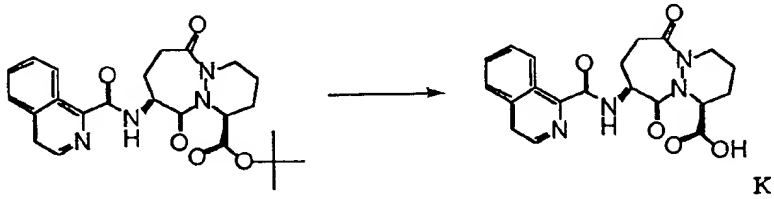
B.



I' J'

t-Butyl-9-(isoquinolin-1-oylamino) -6, 10-dioxo-1,2,3,4,7,8,9,10-octahydro-6-H-pyridazino[1,2-a][1,2] diazepine-1-carboxylate To a solution of the amine I' (79 g, 0.265 mol) and isoquinolin-1-carboxylic acid (56g, 0.32 mol) in dichloromethane:DMF (400mL:400mL) was added hydroxybenztriazole (54 g, 0.4 mol) and 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (74 g, 0.39 mol) and the resulting mixture was allowed to stir at ambient temperature for 16 hours. The reaction mixture was poured into water and extracted with ethyl acetate. The ethyl acetate layer was washed with 0.5N sodium bisulfate, water, sodium bicarbonate, brine, dried over sodium sulfate and concentrated *in vacuo* to afford 122 g of compound J' as an orange solid-foam.

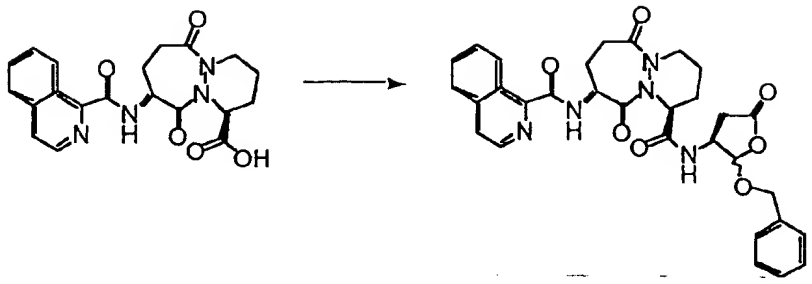
C.



J' K'

9-(isoquinolin-1-oylamino) -6, 10-dioxo-1,2,3,4,7,8,9,10-octahydro-6-H-pyridazino[1,2-a][1,2] diazepine-1-carboxylate A solution of the ester J' (122 g) in dichloromethane and trifluoroacetic acid (200 mL) was allowed to stir at ambient temperature for 16 hours. The reaction mixture was concentrated to a black oil which was then triturated with acetonitrile and ether to afford 98 g of compound K' as a pale yellow solid.

D.



K′ L′

[1S, 9S (2RS, 3S)] N-(2-benzyloxy-5-oxotetrahydrofuran-3-yl)-6,10-dioxo-9-(isoquinolin-1-oylamino)-1,2,3,4,7,8,9,10-octahydro-6-H-pyridazino[1,2-a][1,2] diazepine-1-carboxamide To a solution of (3S, 2RS) 3-allyloxycarbonylamino-2-(4-chlorobenzyl)oxy-5-oxotetrahydrofuran [Bioorg. & Med. Chem. Lett., 2, pp. 615-618 (1992)] (4.4 g, 15.1 mmol) in dichloromethane was added N,N-dimethylbarbituric acid (5.9g, 3.8 mmol) then tetrakispalladium(0) triphenyl phosphine (1.7 g, 1.5 mmol) and the resulting mixture was allowed to stir at ambient temperature for 15 minutes. To the resulting mixture was added the acid, compound K′ (5.0 g, 12.6 mmol), hydroxybenztriazole(2.0 g, 14.8 mmol) then and 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (2.7g, 14 mmol) and the reaction was allowed to stir for 3 hours at ambient temperature. The reaction mixture was then poured into water and extracted with ethyl acetate. The organics were washed with 0.5M sodium bisulfate, water, sodium bicarbonate, brine, dried over magnesium sulfate and concentrated *in vacuo* to afford 2.6 g of the crude product as a yellow foam. The crude material was purified by column chromatography (SiO_2, dichloromethane:acetone 9:1 - 3:1) to afford 1.2 g of the compound L′.

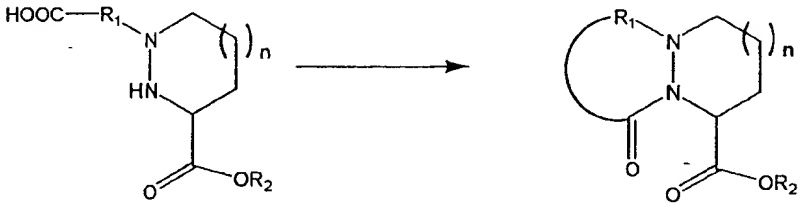
Compound L' and related compounds that may be synthesized using the method of this invention as an intermediate step are described in WO 97/22619, the disclosure of which is herein incorporated by reference. Those related compounds may be synthesized from the product of the method of this invention, H or H', through modifications of the procedure set forth in Example 2. Such modifications are well known in the art.

While we have hereinbefore presented a number of embodiments of this invention, it is apparent that my basic construction can be altered to provide other embodiments which utilize the methods of this invention. Therefore, it will be appreciated that the scope of this invention is to be defined by the claims appended hereto rather than the specific embodiments which have been presented hereinbefore by way of example.

CLAIMS

We claim:

1. A process for converting compound G to compound H:



G H

wherein:

R_1 is a C2-C4 straight chain alkyl optionally substituted at any carbon with one or more substituents selected from C1-C6 straight or branched alkyl, C2-C6 straight or branched alkenyl or alkynyl, O-C1-C6 straight or branched alkyl, O-C2-C6 straight or branched alkenyl or alkynyl, oxo, halo, NO_2, $N(R_4)(R_4)$, CN, Ar or O-Ar;

R_2 is selected from hydrogen, C1-C6 straight or branched alkyl, C2-C6 straight or branched alkenyl or alkynyl C1-C6 alkyl or Ar, wherein said alkyl, alkenyl or alkynyl is optionally substituted with Ar;

n is 0 or 1;

Ar is a saturated, partially saturated or unsaturated monocyclic or bicyclic ring structure, wherein each ring contains 5 to 7 ring atoms and each ring optionally contains from 1 to 3 heteroatoms selected from O, N and S;

wherein Ar is optionally substituted at one or more ring atoms with one or more substituents independently selected from C1-C6 straight or branched alkyl, C2-C6 straight or branched alkenyl or alkynyl, O-C1-C6 straight or branched alkyl, O-C2-C6 straight or branched alkenyl

or alkynyl, oxo, halo, NO_2, $N(R_4)(R_4)$, CN, Ar_1, $O-Ar_1$; wherein

Ar_1 is a saturated, partially saturated or unsaturated monocyclic or bicyclic ring structure, wherein each ring contains 5 to 7 ring atoms and each ring optionally contains from 1 to 3 heteroatoms selected from O, N and S; and

each R_4 is independently selected from H or an amino protecting group, with the proviso that both R_4 are not simultaneously hydrogen, said process comprising the steps of:

(a) suspending compound G in an organic solvent selected from dichloroethane, dichloromethane, toluene, chlorobenzene, chloroform, monoglyme, diglyme or CCl_4;

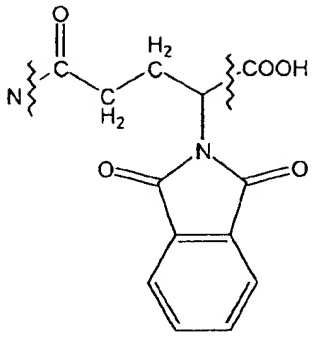
(b) adjusting the temperature of the resulting solution to between 20°C and 100°C;

(c) adding 2 to 4 equivalents of base and more than about 1 equivalent of RSO_pCl_p to said solution, wherein R is absent or selected from C1-C6 straight or branched alkyl or Ar, and each p is independently 1 or 2; and

(d) incubating said solution over a period of between 2 and 18 hours.

2. The process according to claim 1, wherein R_1 is substituted at the terminal carbon bound to the COOH moiety with a nitrogen-containing moiety that can be chemically modified to an amine.

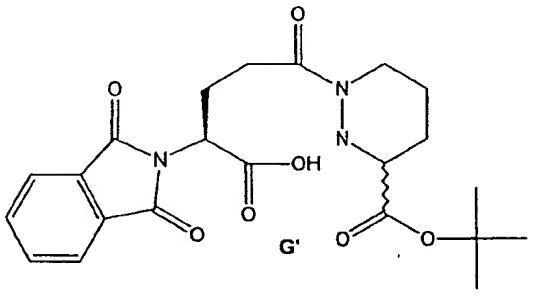
3. The process according to claim 2, wherein R_1 is:



4. The process according to claim 1, wherein n is 1.

5. The process according to claim 1, wherein R_2 is t-butyl.

6. The process according to claim 5, wherein compound G has the formula:



G'

7. The process according to claim 1, wherein in step (a) the organic solvent is dichloroethane.

8. The process according to claim 1, wherein step (b) is carried out at about 70°C.

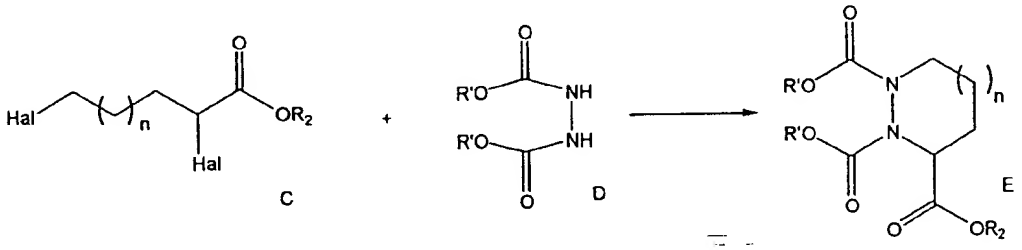
9. The process according to claim 1, wherein in step (c) about 2 equivalents of RSO_pCl_p are used.

10. The process according to claim 9, wherein RSO_pCl_p is methanesulfonyl chloride or $SOCl_2$.

11. The process according to claim 1, wherein said base is selected from pyridine, collidine, lutidine, $NaHCO_3$, imidazole, triethylamine, N-methylmorpholine, diisopropylethylamine or K_2CO_3.

12. The process according to claim 11, wherein said base is 2,6-lutidine.

13. A process for producing compound E by reacting compounds C and D:



comprising the steps of:

a) dissolving compounds C and D together in DMF;

b) adding to said solution of C and D:

i) a water scavenger;

ii) a metal hydroxide selected from LiOH, NaOH or KOH; and

iii) a phase transfer catalyst

c) allowing the mixture produced in step b) to react at room temperature for 2 to 48 hours;

d) adding an organic solvent and water to said mixture to create an aqueous phase and an organic phase; and

e) purifying compound E from said organic phase; wherein:

R_2 is selected from hydrogen, C1-C6 straight or branched alkyl, C2-C6 straight or branched alkenyl or alkynyl C1-C6 alkyl or Ar, wherein said alkyl, alkenyl or alkynyl is optionally substituted with Ar;

n is 0 or 1;

"Hal" is any halogen; and

each R' is an independently selected carboxyl protecting group.

14. The process according to claim 13, wherein said water scavenger is sodium sulfate.

15. The process according to claim 13, wherein said metal hydroxide is LiOH.

16. The process according to claim 13, wherein said phase transfer catalyst is Bu_4NI.

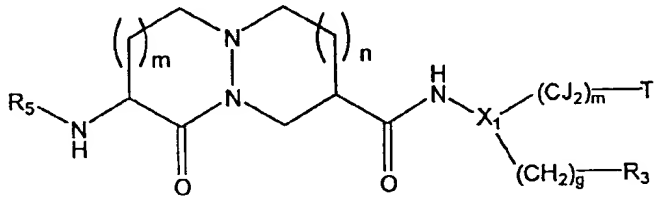
17. The process according to claim 13, wherein n is 1.

18. The process according to claim 13, wherein each Hal is Br.

19. The process according to claim 13, wherein R_2 is t-butyl.

20. The process according to claim 13, wherein R' is benzyl.

21. The process according to claim 1 or 13, wherein said process is used as a step in the synthesis of a compound (I) having the formula:



(I)

wherein:

any ring is optionally substituted at any carbon by Q_1, at any nitrogen by R_5, and at any atom by =O, -OH, -COOH, or halogen;

X_1 is CH or N;

g is 0 or 1;

m is 0, 1 or 2;

n is 0 or 1;

each J is independently selected from -H, -OH, or -F, provided that when a first and a second J are bound to a C, and said first J is -OH, then said second J is -H;

T is $-Ar_3$, -OH, $-CF_3$, -C(O)-C(O)-OH, -C(O)-OH or any biosteric replacement for -C(O)-OH;

R_3 is -CN, $-CH=CH-R_9$, $CH=N-O-R_9$, $-(CH_2)_{1-3}-T_1-R_9$, $-CJ_2-R_9$, $-C(O)-R_{13}$, or $-C(O)-C(O)-N(R_5)(R_{10})$;

T_1 is -CH=CH-, -O-, -S-, -SO-, $-SO_2-$, $-NR_{10}-$, $-NR_{10}-C(O)-$, -C(O)-, -O-C(O)-, -C(O)-O-, $-C(O)-NR_{10}-$, $O-C(O)-NR_{10}-$, $-NR_{10}-C(O)-O-$, $-NR_{10}-C(O)-NR_{10}-$, $-S(O)_2-NR_{10}-$, $-NR_{10}-S(O)_2-$ or $-NR_{10}-S(O)_2-NR_{10}-$;

each R_5 is independently selected from -H, $-Ar_1$, $-C(O)-Ar_1$, $-S(O)_2-Ar_1$, $-R_9$, $-C(O)-NH_2$, $-S(O)_2-NH_2$, $-C(O)-R_9$,

$-C(O)-O-R_9$, $-S(O)_2-R_9$, $-C(O)-N(R_{10})(Ar_1)$, $-S(O)_2-N(R_{10})(Ar_1)$, $-C(O)-N(R_{10})(R_9)$, or $-S(O)_2-N(R_{10})(R_9)$;

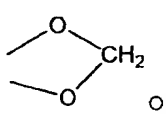
each R_9 is a C_{1-6} straight or branched alkyl group optionally singly or multiply substituted with -OH, -F, =O or Ar_1, wherein any R_9 may be substituted with a maximum of two Ar_1;

each R_{10} is independently selected from -H or C_{1-6} straight or branched alkyl;

R_{13} is -H, $-Ar_1$, $-R_9$, $-T_1-R_9$ or $-(CH_2)_{1-3}-T_1-R_9$;

each Ar_1 is a cyclic group independently selected from a monocyclic, bicyclic or tricyclic aryl group containing 6, 10, 12 or 14 carbon atoms; a monocyclic, bicyclic or tricyclic cycloalkyl group containing between 3 and 15 carbon atoms, said cycloalkyl group being optionally benzofused; or a monocyclic, bicyclic or tricyclic heterocycle group containing between 5 and 15 ring atoms and at least one heteroatom group selected from -O-, -S-, -SO-, $-SO_2-$, =N-, or -NH-, wherein said heterocycle group optionally contains one or more double bonds and optionally comprises one or more aromatic rings;

Ar_3 is a cyclic group selected from phenyl, a 5-membered heteroaromatic ring or a 6-membered heteroaromatic ring, wherein said heteroaromatic rings comprise from 1-3 heteroatom groups selected from -O-, -S-, -SO-, $-SO_2-$, =N-, or -NH-;

wherein each Ar_1 or Ar_3 is optionally singly or multiply substituted at any ring atom by $-NH_2$, $-C(O)-OH$, -Cl, -F, -Br, -I, $-NO_2$, -CN, =O, -OH, -perfluoro C_{1-3} alkyl,  or $-Q_1$; and

each Q_1 is independently selected from $-Ar_1$, $-R_9$, $-T_1-R_9$, or $(CH_2)_{1-3}-T_1-R_9$; provided that when $-Ar_1$ is substituted with a Q_1 which comprises one or more additional $-Ar_1$ groups, said additional $-Ar_1$ groups are not substituted with Q_1.

22. The process according to claim 21, wherein m is 2 and n is 1.

23. The process according to claim 22, wherein the terminal R_5 is selected from $-C(O)-Ar_1$, $-C(O)-NH_2$, $-C(O)-R_9$, $-C(O)-O-R_9$, $-C(O)-N(R_{10})(Ar_1)$, or $-C(O)-N(R_{10})(R_9)$.

24. The process according to claim 23, wherein:

X_1 is CH;

each J is H;

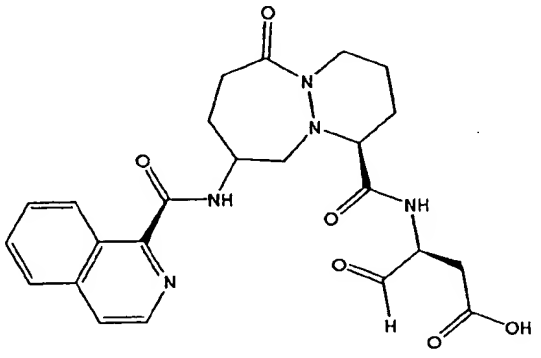
m' is 1;

T is -COOH or a biosteric replacement for -COOH;

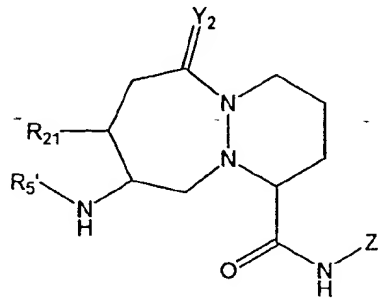
g is 0; and

R_3 is $-C(O)-R_{13}$.

25. The process according to claim 21, wherein compound I has the structure:



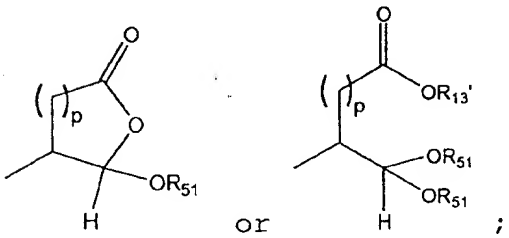
26. The process according to claim 4 or 17, wherein said process is used as a step in the synthesis of a compound of the formula (II):



(II);

wherein:

Z is selected from



;

p is 1 or 2;

each $R_{5'}$ is independently selected from $-C(O)-R_{10'}$, $-C(O)O-R_{9'}$, $-C(O)-N(R_{10'})(R_{10'})$, $-S(O)_2-R_{9'}$, $-S(O)_2-NH-R_{10'}$, $-C(O)-CH_2-O-R_{9'}$, $-C(O)C(O)-R_{10'}$, $-R_{9'}$, $-H$, $-C(O)C(O)-OR_{10'}$, or $-C(O)C(O)-N(R_{9'})(R_{10'})$;

each $R_{9'}$ is independently selected from $-Ar_1$ or a $-C_{1-6}$ straight or branched alkyl group optionally substituted with Ar_1, wherein the $-C_{1-6}$ alkyl group is optionally unsaturated;

each $R_{10'}$ is independently selected from $-H$, $-Ar_1$, a $-C_{3-6}$ cycloalkyl group, or a $-C_{1-6}$ straight or branched alkyl group optionally substituted with $Ar_{3'}$, wherein the $-C_{1-6}$ alkyl group is optionally unsaturated;

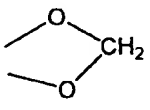
$R_{13'}$ is selected from H, Ar_1, or a C_{1-6} straight or branched alkyl group optionally substituted with Ar_1, $-CONH_2$, $-OR_{5'}$, -OH, $-OR_{9'}$, or $-CO_2H$;

each R_{51} is independently selected from $R_{9'}$, $-C(O)-R_{9'}$, $-C(O)-N(H)-R_{9'}$, or two R_{51} taken together form a saturated 4-8 member carbocyclic ring or heterocyclic ring containing -O-, -S-, or -NH-;

each R_{21} is independently selected from -H or a $-C_{1-6}$ straight or branched alkyl group;

Y_2 is $-H_2$ or =O

each Ar_1 is a cyclic group independently selected from the set consisting of an aryl group which contains 6, 10, 12, or 14 carbon atoms and between 1 and 3 rings and an aromatic heterocycle group containing between 5 and 15 ring atoms and between 1 and 3 rings, said heterocyclic group containing at least one heteroatom group selected from -O-, -S-, -SO-, SO_2, =N-, and -NH-, said heterocycle group optionally containing one or more double bonds, said heterocycle group optionally comprising one or more aromatic rings, and said cyclic group optionally being singly or multiply substituted by $-Q_1$; and

each Q_1 is independently selected from the group consisting of $-NH_2$, $-CO_2H$, -Cl, -F, -Br, -I, $-NO_2$, -CN, =O, -OH, -perfluoro C_{1-3} alkyl, $R_{5'}$, $-OR_{5'}$, $-NHR_{5'}$, $OR_{9'}$, $-N(R_{9'})(R_{10'})$, $R_{9'}$, $-C(O)-R_{10'}$, and 

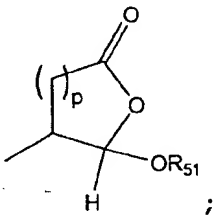
;

provided that when $-Ar_1$ is substituted with a Q_1 group which comprises one or more additional $-Ar_1$ groups, said additional $-Ar_1$ groups are not substituted with another $-Ar_1$.

27. The process according to claim 26, wherein in compound II, Y_2 is O and R_{21} is H.

28. The process according to claim 26, wherein in compound II, $R_{5'}$ is selected from $-C(O)-R_{10'}$, $-C(O)O-R_{9'}$, $-C(O)-N(R_{10'})(R_{10'})$, $-C(O)-CH_2-O-R_{9'}$, $-C(O)C(O)-R_{10'}$, $-C(O)C(O)-OR_{10'}$, or $-C(O)C(O)-N(R_{9'})(R_{10'})$.

29. The process according to claim 26, wherein in compound II,

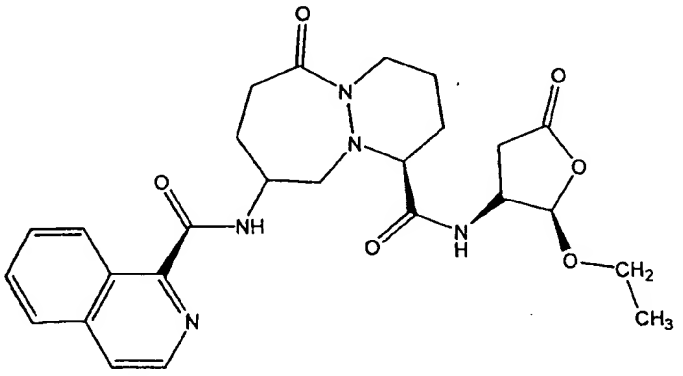


Z is ;

p is 1; and

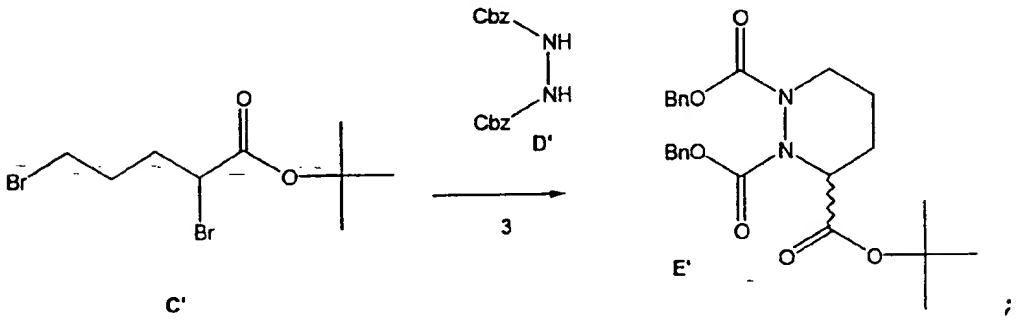
R_{51} is selected from $-Ar_1$, $-C_{1-6}$ straight or branched alkyl or $-C_{1-6}$ straight or branched alkyl substituted with Ar_1.

30. The process according to claim 26, wherein compound II has the structure:



31. The process according to claim 30, comprising the steps of:

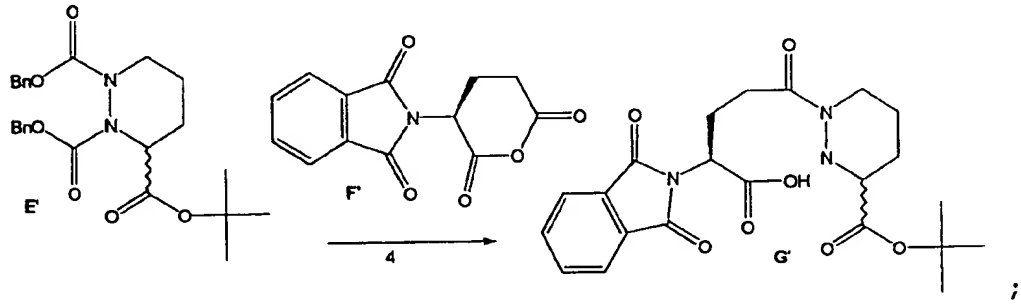
a) reacting compound C′ and compound D′ together in DMF in the presence of sodium sulphate, LiOH and Bu_4NI and in the absence of oxygen to produce compound E′:



;

b) dissolving E′ in THF in the absence of oxygen, adding triethylamine and $Pd(OAc)_2$, and allowing reaction to proceed for 12 to 24 hours;

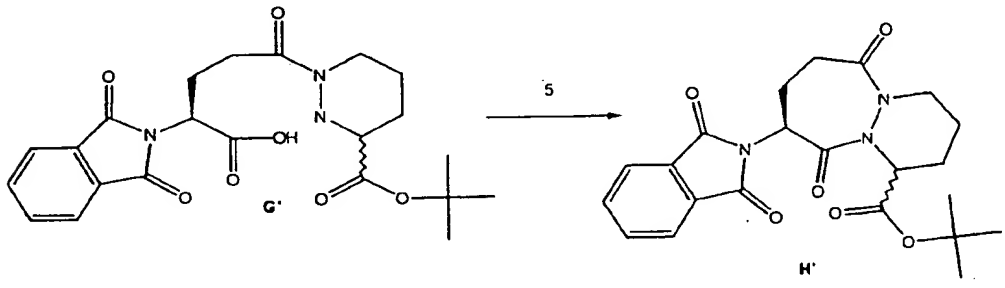
c) adding to said solution produced in step b) aqueous sodium bicarbonate and compound F′ to produce compound G′:



;

and

d) suspending compound G′ in dichloroethane at between 50°C and 80°C, and adding 2,6-lutidine and methanesulfonyl chloride to produce compound H′:



INTERNATIONAL SEARCH REPORT

Inter: nal Application No
PCT/US 99/19080

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 C07D237/04 C07D487/04

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 C07D

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	US 4 692 438 A (HASSALL ET. AL.) 8 September 1987 (1987-09-08) column 3, line 65 -column 4, line 12; example 1 ---	1-12
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A	WO 94 11353 A (UNIVERSITY COLLEGE LONDON) 26 May 1994 (1994-05-26) page 5, line 18 -page 7, line 25; claims; examples --- -/--	13-20

[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

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Date of the actual completion of the international search	Date of mailing of the international search report
7 December 1999	27/12/1999

Name and mailing address of the ISA	Authorized officer
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Inter nal Application No
PCT/US 99/19080

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

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